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| 09/870,012 | 05/29/2001 | Chaitan Khosla | 300622000213 | 9415 |

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| EXAMINER |
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KERR, KATHLEEN M

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| ART UNIT | PAPER NUMBER |
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1652

DATE MAILED: 07/01/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

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|-----------------------------|-----------------------------|------------------|
| Offic Action Summary | Application No. | Applicant(s) |
| | 09/870,012 | KHOSLA ET AL. |
| | Examiner Kathleen M Kerr | Art Unit 1652 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 21 April 2003.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4) Claim(s) 18-21,23 and 24 is/are pending in the application.

4a) Of the above claim(s) 18 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 19-21,23 and 24 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. _____.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

| | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (Paper No. 8, mailed on December 3, 2002), Applicants filed an amendment and response received on April 21, 2003 (Paper No. 10). Said amendment amended Claims 19, 20, 23, and 24 and cancelled Claim 22. Thus, Claims 18-21 and 23-24 are pending in the instant Office action.

Claim 18 remains withdrawn from consideration as a non-elected invention (election by Applicants without traverse in Paper No. 7). Claims 19-21 and 23-24 will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/003,338 filed on July 6, 1995 and the U.S. non-Provisional Application No. 08/675,817 (now USPN 6,080,555) filed on July 5, 1996. Neither of these applications, however, disclosed the claimed invention of Claims 19-24.

The instant application is granted the benefit of priority for the U.S. non-Provisional Application No. 08/896,323 (USPN 6,066,721) filed on July 17, 1997 and the U.S. non-Provisional Application No. 08/434,289 (now USPN 6,261,816) filed on November 5, 1999. These applications do disclose the claimed invention. Thus, the earliest effective filing date of the claimed invention is considered to be July 17, 1997.

Withdrawn - Objections to the Specification

3. Previous objection to the specification for lacking updated continuity data in the first paragraph is withdrawn by virtue of Applicant's amendment.
4. Previous objection to the specification because the title is not descriptive is withdrawn by virtue of Applicant's amendment to the specification.
5. Previous objection to the Abstract for not completely describing the disclosed subject matter is withdrawn by virtue of Applicants' amendment.

Withdrawn - Claim Objections

6. Previous objection to Claim 24 for omitting where the structure of Formula 7 can be found in the specification is withdrawn by virtue of Applicants' amendment to Claim 24.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

7. Previous rejection of Claims 22 and 24 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviation "6-dEB" is withdrawn by virtue of Applicants' amendment.

Maintained - Claim Rejections - 35 U.S.C. § 112

8. Previous rejection of Claims 19-21 and 23-24 under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms "macrolide" and "antibiotic" is maintained, in modified form so as to apply to the amended term "macrolactone" now found in the claims. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that the amendment obviates the rejection since the term "macrolactone" is clear and well-defined as

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being distinct from antibiotics. The Examiner disagrees. Macrolactones are heterocyclic structures having multiple lactone functional groups; erythromycin also falls into this description. Thus, it is unclear “When exactly does a [macrolactone] become an antibiotic in its biosynthesis? As soon as it has any anti-bacterial activity? Most antibiotic precursors could fall into this broad definition. Thus, the metes and bounds of the terms are unclear. Appropriate clarification is required” (see previous Office action).

9. Previous rejection of Claim 20 under 35 U.S.C. § 112, first paragraph, written description, is maintained. Applicants’ arguments have been fully considered but are not deemed persuasive for the following reasons. Applicants argue the enablement of the mutants required to practice the claimed methods. However, at issue is the description found in the specification of the structure of all reagents used in the methods so that one of skill in the art would agree that Applicants were in possession of the *genus* of the claimed invention. A purely functional description of the cells used in the methods is inadequate to describe the *genus* because no relation between structure and function is described in the specification in support of the *genus*. Thus, it is maintained that the instant claim is not described to the full extent of its scope in the specification as originally filed.

10. Previous rejection of Claim 21 under 35 U.S.C. § 112, first paragraph, enabling deposit, is maintained; this rejection as drawn to Claims 21 and 22-24 is withdrawn by virtue of Applicants’ amendment. Applicants’ arguments concerning the rejection of Claim 21 have been fully considered but are not deemed persuasive. Applicants argue that the obtaining of mutants is described in the search for markers. However, Claim 21 requires the use of exactly the strain

A34. If the experiments of Weber *et al.* were repeated by those of skill in the art, a different mutant is likely to be obtained having the same function but not necessarily the same structure. Since A34, *per se*, is required for Claim 21, a deposit of the exact strain, or some other means of enabling the exact strain, is required. So, to repeat, “to practice the instant methods, one of skill in the art is required to use the A34 mutant. It is not clear from Weber *et al.* how to make the A34 mutant using publicly available resources. Thus, its deposit is required. To enable the instant claims by enabling the deposit of A34, the following items are required: (1) the accession number assigned by the depository, (2) the date of deposit, (3) a brief description of the deposit, (4) the name and full address of the depository (37 C.F.R. § 1.801 - 1.809), and (5) the record must also contain a statement certifying that all restrictions on accessibility to said deposit be irrevocably removed by Applicant upon the granting of the patent (see M.P.E.P. § 2404.01); this statement may be certified by Applicants or Applicants’ representative.”

Maintained - Claim Rejections - 35 U.S.C. § 102

11. Previous rejection of Claims 19 and 20 under 35 U.S.C. § 102(e) as being anticipated by Katz *et al.* (USPN 5,824,513) is maintained. Applicants’ arguments have been fully considered but are not deemed persuasive in view of the unclear definition of “macrolactone”. See also new matter rejection below. The previous rejection is reiterated below for completeness:

“Claims 19 and 20 are rejected under 35 U.S.C. § 102(e) as being anticipated by Katz *et al.* (USPN 5,824,513). The instant claims are drawn to methods of making antibiotics using a mutant *Saccharopolyspora erythraea* host cells that has been fed a macrolide that acts as a precursor in the biosynthetic pathway of the antibiotic.

Katz *et al.* teach “alterations which will result in the production of macrolide rings only when fed exogenously with substrate analogs, e.g. thioesters of appropriate acyl compounds of various lengths” (see column 4, lines 9-15). More specifically, in Examples 19-21, a mutant *S. erythraea* AKS1, whose KS1

allele has been mutated in its chromosome, is fed a butyl thioester of a δ -lactone to produce an antibiotic as tested by the antibiotic-sensitive microorganism, *S. aureus* (see columns 13-14)."

NEW REJECTIONS

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 19-21 and 23-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear how the adjectives in "heterologously and recombinantly produced macrolactone polyketide" help define the macrolactone compound added to the culture. In view of Applicants remarks concerning the entry of this phrase, the Examiner suggests writing the claim with a method step of making the macrolactone compound in a host cell previous to its addition for clarity of the terms.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 19-21 and 23-24 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

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skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims gather their support only from Example 4 as originally filed. In Example 4, mutant A34 is fed 6-dEB and makes an unnamed antibiotic, and mutant A34 is fed compounds 6 and 7 and produces compounds 10 and 11, respectively, as evidenced after extraction. There is no support in Example 4 for the following concepts found in the claims:

- a) for adding a step of producing a macrolactone heterologously and recombinantly since Example 4 just uses compounds 6 and 7 without regard to their production
- b) for generic genus of macrolactone – the word is only found on page 1, line 23
- c) for subset that is “other than 6-dEB” since this experiment is found in the Example where support is indicated
- d) for doing this in **any** *S. erythraea* since it is only performed in the mutant A34
- e) for a genus of *S. erythraea* mutants that don’t produce macrolactone polyketides (Claim 20)
- f) for the subgenus of 14-member macrolactone polyketides (Claim 23)

No indication that any genus, such as those enumerated above, was envisioned as an invention when originally filed.

The Examiner notes that if Claim 24 depended from Claim 20, support would be found in the specification for such a claim.

14. Claims 23 and 24 are rejected under 35 U.S.C. § 112, first paragraph, written description, as maintained above for Claim 20. Applicants’ arguments as pertaining to claim 20 have been answered above. The previous rejection is reiterated below for completeness:

“Claim 20 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 20 is drawn to methods of using *S. erythraea*, wherein said cells are described only by function, i.e., producing no macrolide.

The Court of Appeals for the Federal Circuit has recently held that a “written description of an invention involving a chemical genus, like a

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description of a chemical species, ‘requires a precise definition, such as be structure, formula [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, a single example of an *S. erythraea* cell that produces no macrolide is described in the form of the A34 mutant taught by *Weber et al.* No structural information about this mutant is described. While methods using this particular mutant strain are adequately described in the specification, the specification is wholly devoid and any structure of mutants to be used in the instant claim so that one of skill in the art would be able to predict the structure of other members of the genus of cell strains used in the claims. Thus, the instant claim is not described to the full extent of its scope in the specification as originally filed.”

Summary of Pending Issues

15. The following is a summary of the issues pending in the instant application:

- a) Claims 19-21 and 23-24 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms “macrolide” and “antibiotic”.
- b) Claims 19-21 and 23-24 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the adjectives in “heterologously and recombinantly produced macrolactone polyketide”.
- c) Claims 20, 23, and 24 stand rejected under 35 U.S.C. § 112, first paragraph, written description.
- d) Claim 21 stands rejected under 35 U.S.C. § 112, first paragraph, enabling deposit.
- e) Claims 19-21 and 23-24 stand rejected under 35 U.S.C. § 112, first paragraph, new matter.
- f) Claims 19 and 20 stand rejected under 35 U.S.C. § 102(e) as being anticipated by *Katz et al.* (USPN 5,824,513).

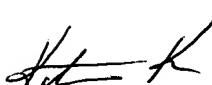
Conclusion

16. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. The instant Office action is **non-Final** because the new matter issues should have been previously addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


KMK
June 29, 2003